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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/930,494
Filing Date: August 16, 2001
Appellant(s): VON BORSTEL ET AL.

Leonard C. Mitchard
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed May 17, 2007 appealing from the Office action mailed April 12, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,316,426B1	VON BORSTEL	11-2001
2005/0123922 A1	CATTANEO	6-2005

Bren "Alzheimer's: Searching for a Cure" FDA Consumer Magazine, July-August 2003 Issue, Pub. No. FDA 04-1318C rev.

Hollander et al. Am. J. Psychiatry (1999), Vol. 156:2, pages 317-320

Page et al. Proc. Natl. Acad. Sci. USA (1997), Vol. 94, pages 11601-11606

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-15, 18-32, and 47-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of congenital mitochondrial disease, Alzheimer's Disease, Huntington's Disease, neuromuscular degenerative disease, and pathophysiological consequences of mitochondrial respiratory chain dysfunction, does not reasonably provide enablement for the prevention of congenital mitochondrial disease, Alzheimer's Disease, Huntington's Disease, neuromuscular degenerative disease, and pathophysiological consequences of mitochondrial respiratory chain dysfunction. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in In re Wands, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

The factors include, but are not limited to:

1. The breadth of the claims,
2. The nature of the invention,
3. The state of the prior art,
4. The level of one of ordinary skill,
5. The level of predictability in the art,
6. The amount of direction provided by the inventor,
7. The existence of working examples, and
8. The quantity of experimentation needed to make and/or use the invention based on the content of the disclosure.

Claims 1-15, 18-32, and 47-49 are drawn to a method for treating or preventing pathophysiological consequences of mitochondrial respiratory chain dysfunction in a mammal comprising administering an effective amount of a pyrimidine nucleotide. Claims 2-15 limit cause of the respiratory chain dysfunction. Claims 18-21 limit the mode of administration of the active agent. Claims 22-32 limit the conditions treated or prevented. Claims 47-49 further require the administration of pyruvic acid, a pharmaceutically acceptable salt thereof, or a pyruvic acid ester.

The nature of the invention requires a close look at that which is provided in the claims and the scope of the content encompassed by the claim language. The instantly claimed invention relates to compounds and methods for treatment and prevention of diseases, developmental delays, and symptoms related to mitochondrial dysfunction. Pyrimidine nucleotide precursors are administered to a mammal, including a human, for the purpose of compensating for mitochondrial dysfunction and for improving mitochondrial functions.

The treatment of diseases involving mitochondrial dysfunction is well known in the art. Treatment generally involves the administration of vitamins and cofactors used by particular elements of the mitochondrial respiratory chain.

A person of ordinary skill in the art would be a M.D. or a medicinal chemist having a PhD degree or higher.

In the instant case, examples drawn to treatment are not seen as sufficient to support the alleged applicability for the prevention of congenital mitochondrial disease, Alzheimer's Disease, Huntington's Disease, neuromuscular degenerative disease, and pathophysiological consequences of mitochondrial respiratory chain dysfunction. Insufficient data has been presented which demonstrates that congenital mitochondrial disease, Alzheimer's Disease, Huntington's Disease, neuromuscular degenerative disease, or pathophysiological consequences of mitochondrial respiratory chain dysfunction is prevented by the administration of a pyrimidine nucleotide precursor as instantly claimed.

It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use if for themselves, see In re Gardneret al, 166 USPQ 138 (CCPA 1970). Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the prevention of congenital mitochondrial disease, Alzheimer's disease, Huntington's disease, neuromuscular degenerative disease, and pathophysiological consequences of mitochondrial respiratory chain dysfunction.

Claims 33-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 33-36 are drawn to a method for preventing death or functional decline of, post-mitotic cells in a mammal due to mitochondrial respirator chain dysfunction comprising administration of an effective amount of a pyrimidine nucleotide precursor. Claims 34-36 limit the nature of said post-mitotic cells.

The nature of the invention requires a close look at that which is provided in the claims and the scope of the content encompassed by the claim language. The instantly claimed invention relates to compounds and methods for treatment and prevention of diseases, developmental delays, and symptoms related to mitochondrial dysfunction. Pyrimidine nucleotide precursors are administered to a mammal, including a human, for

the purpose of compensating for mitochondrial dysfunction and for improving mitochondrial functions.

The treatment of diseases involving mitochondrial dysfunction is well known in the art. Treatment generally involves the administration of vitamins and cofactors used by particular elements of the mitochondrial respiratory chain.

A person of ordinary skill in the art would be a M.D. or a medicinal chemist having a PhD degree or higher.

In the instant case, examples drawn to treatment is not seen as sufficient to support the alleged applicability for the prevention of death or functional decline of post-mitotic cells. Insufficient data has been presented which demonstrates that death or functional decline of post-mitotic cells is prevented by the administration of a pyrimidine nucleotide precursor as instantly claimed.

It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use if for themselves, see *In re Gardner et al,* 166 USPQ 138 (CCPA 1970). Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the prevention of death or functional decline pf post-mitotic cells in a mammal.

Claims 1-15, 18-32, and 37-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Page et al. Proc. Natl. Acad. Sci. USA, 1997, Vol. 94, pages 11601-11606 (Page) in combination with von Borstel et al. U.S. Patent 6,316,426 B1 (von Borstel).

Claims 1-15 and 18-32 are drawn to a method for treating or preventing pathophysiological consequences of mitochondrial respiratory chain dysfunction in a mammal comprising administering an effective amount of a pyrimidine nucleotide. Claims 2-15 limit cause of the respiratory chain dysfunction. Claims 18-21 limit the mode of administration of the active agent. Claims 22-32 limit the conditions treated or prevented. Claims 37-41 are drawn to a method for treating developmental delay in cognitive, motor, language, executive function, or social skills in a mammal comprising administration of an effective amount of a pyrimidine nucleoside.

Page teaches the treatment of patients described with a syndrome that included developmental delay, seizures, ataxia, recurrent infections, severe language deficit, and an unusual behavioral phenotype characterized by hyperactivity, short attention span, and poor social interaction with uridine (Abstract). Patients were treated with 50-1,000 mg/kg per day uridine (page 11604, column 2).

Page differs from the instantly claimed invention in that Page does not teach the use of acyl derivatives of uridine nor does Page explicitly teach all the conditions within the scope of the instantly claimed invention. However, these deficiencies would have

been obvious to one of ordinary skill in the art at the time of the invention when viewed in combination with von Borstel.

von Borstel teaches a family of uridine and cytidine derivatives for the treatment of a variety of disorders including heart, muscle, plasma, liver, bone, diabetic, and neurological conditions (column 8, lines 20-24). The acyl derivatives of uridine comprise compounds having the formula (11) wherein R is an acyl radical of an unbranched fatty acid, an amino acid, a dicarboxylic acid, or a carboxylic acid selected from one or more of the group consisting of glycolic acid, pyruvic acid, orotic acid, and creatine (column 9. lines 1-23). 2',3'5'-tri-O-acetyl uridine is taught as being a preferred active agent (column 10, lines 2-5). The invention contemplates the use of these acyl derivatives for treating a variety of physiological and pathological conditions, including treatment of cardiac insufficiency and myocardial infarction, treatment of liver disease or damage, muscle performance, treatment of lung disorders, diabetes, central nervous system disorders such as cerebrovascular disorders, Parkinson's disease, and senile demetias (column 10 lines 24-35).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat patients having a mitochondrial disease with an acylated derivative of uridine as taught by the prior art. The examiner recognizes that all of the conditions listed as being treatable/preventable by the instant uridine compounds are not explicitly embraced by the prior art; however, applicant has merely found a new property of the instant uridine compounds and such a discovery does not constitute a new use. In the instant case, the population to be treated is a subject having a mitochondrial disease.

The prior art teaches the treatment of this population with an acylated derivative of uridine rendering the instantly claimed method *prima facie* obvious.

(10) Response to Argument

Rejections under 35 U.S.C. 112, first paragraph

Applicant argues that the idea of prevention does not relate to preventing or reversing genetic defects but, rather, compensating for them to prevent full clinical manifestation of their disorder. Applicant has further cited references to support applicant's arguments.

Applicant's arguments relating to the Saydoff et al., Gines et al. and any other publication published after the effective filing date of the instant application have been noted but are not sufficient to overcome the instant rejection. Whether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. In general, if an applicant seeks to use a publication to prove the state of the art for the purpose of the enablement requirement, the publication must have been published (made available to the public) earlier than the effective filing date of the application.

Applicant's assertion that the understanding of one of ordinary skill in the art would not have changed significantly over the period of time from 1998 to 2003 has also been noted, however during patent examination, the pending claims must be given their broadest reasonable interpretation consistent with the specification. This means that the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the specification. In the instant case, the specification does not provide a definition of "prevention". In the absence of an express intent to impart a novel meaning to the claim terms, the words are presumed to take on the ordinary and customary meanings attributed to them by those of ordinary skill in the art. Furthermore the claims are rejected under 35 U.S.C. 112, first paragraph, because the disclosure is not enabled for the prevention of congenital mitochondrial disease, Alzheimer's Disease, Huntington's Disease, neuromuscular degenerative disease, and pathophysiological consequences of mitochondrial respiratory chain dysfunction not because the term "prevention" is indefinite. Applicant's description of the instantly employed compositions as being "neuroprotective" or "cytoprotective" has also been noted; however, said terms are not recited in the instant claims.

As set forth in the previous Office Action dated July 26, 2005, there is a tremendous amount of unpredictability and uncertainty in the art. Bren "Alzheimer's: Searching for a Cure", FDA Consumer Magazine, July-August 2003 Issue, Pub No. FDA 04-1318C rev. (Bren) teaches, "'We are still searching for the sequence of events where we can intervene and cure the disease without causing harm'...The two biggest risk factors for getting AD are age and genetics, neither of which is in our control." Bren

also teaches that therapeutic approaches that are successful in transgenic mice have not been shown to be successful in humans with some actually being harmful. Hollander et al. Am J. Psychiatry (1999), Vol. 156:2, pages 317-320 (Hollander) teaches, "The etiology, pathophysiology, and genetic transmission of autism are not known, but autism may be best understood as a heterogeneous disorder resulting from multiple genetic and environmental factors, often complicated by neurologic, cytogenetic, neurotransmitter, and immunologic abnormalities." The prior art clearly teaches that conditions embraced by the instant claims are not preventable. In the 2003 article, Bren discloses, "No cure or prevention for Alzheimer's disease exists yet...". Cattaneo et al. US 2005/0123922 A1 (Cattaneo) discloses, "At the moment there are no specific therapies available which can prevent symptoms or cure patients affected with Huntington's Disease." See paragraph 0012. Not only does the art teach that many of the conditions are not preventable, the causes are not even known. Indeed, the specification does not provide sufficient support for applicant's claim that Alzheimer's Disease, Huntington's Disease, neuromuscular degenerative diseases, or pathophysiological consequences of mitochondrial respiratory chain dysfunction is prevented by the instant method.

Rejections under 35 U.S.C. 103(a)

Applicant argues that overlapping symptoms are insufficient to establish a prima facie case of obviousness, because it is well recognized that unrelated diseases can have overlapping symptoms.

Applicant's argument that it is not true that all of the conditions recited in the previous Office Action are "necessarily" pathophysiological consequences of mitochondrial respiratory chain dysfunction has been noted; however, the instant methods are drawn to the prevention or treatment of the "consequences" of mitochondrial respiratory chain dysfunction. All of the conditions cited in the prior Office Action are a "consequence" of mitochondrial respiratory chain dysfunction. Therefore, the rejection is still deemed proper. Applicant's argument that unrelated diseases can have overlapping symptoms and that although symptoms may look similar, the treatment will vary according to the underlying problem has also been noted; however, it is not necessary that the prior art recognize a previously unappreciated property of a prior art composition or a scientific explanation for the prior art's functioning.

The references cited by applicant (Lam et al., Krahenbuhl et al., etc.) have been noted; however, in construing process claims and references, it is the identity of manipulative operations which leads to finding of obviousness. In the instant case, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. The USPTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as the would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification. This means that the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the specification. Ordinary, simple English words whose meaning is

clear and unquestionable, absent any indication that their use in a particular context changes their meaning, are construed to mean exactly what they say. While the claims of issued patents are interpreted in light of the specification, prosecution history, prior art and other claims, this is not the mode of claim interpretation to be applied during examination. During examination, the claims must be interpreted as broadly as their terms reasonably allow. The ordinary and customary meaning of the term "prevention" is "to keep from happening : AVERT". The phrase "mammal in need of such treatment or prevention" has not been defined in the instant specification; thus the examiner interprets said phrase to embrace the population treated by Page.

Page teaches the treatment of patients described with a syndrome that included developmental delay, seizures, ataxia, recurrent infections, severe language deficit, and an unusual behavioral phenotype characterized by hyperactivity, short attention span, and poor social interaction with uridine. Developmental delay, seizures, ataxia, recurrent infections, severe language deficit, and an unusual behavioral phenotype characterized by hyperactivity, short attention span, and poor social interaction are "pathophysiological consequences of mitochondrial respiratory chain dysfunction". The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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8/17/07

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